INFLUENCE OF LOCAL RECURRENCE ON THE PROGNOSIS OF SOFT-TISSUE SARCOMAS

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We have investigated the significance of local recurrence on survival in 173 patients with localised soft-tissue sarcomas of the limbs and of the trunk.

The overall survival rates at five and ten years were 75.2% and 68.0%, respectively. After definitive surgery at our hospitals, there was local recurrence in 25 patients (14.5%). After inadequate operations elsewhere, there was a higher incidence of late local recurrence (28.3%), in comparison with those with primary tumours treated by us (9.0%), or patients referred to us immediately after inadequate surgery elsewhere (10.2%). Because of small numbers these differences in the survival rates were not statistically significantly different.

Univariate survival analysis showed that local recurrence after definitive surgery ($p = 0.006$) together with the histological grade ($p = 0.0002$), the size of the tumour ($p = 0.002$), its depth in relation to deep fascia ($p = 0.003$), and the surgical margin ($p = 0.0001$) were the significant prognostic factors. Local recurrence at the initial presentation did not affect survival. Multivariate analysis showed that local recurrence after definitive surgery also lost its apparent prognostic significance.

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Soft-tissue sarcomas (STS) are relatively rare, comprising about 0.7% of all cancers, but 60% to 70% of all tumours arising in the limbs. Over the past two decades, the management of these lesions has changed dramatically. Wide local excision combined with adjuvant radiotherapy, chemotherapy, or both has become standard instead of ablative surgery such as amputation.¹⁻⁴ Unfortunately, inadequate initial surgery of primary tumours is still frequent, before consultation with referral centres. This results in a high incidence of local recurrence, reported as between 50% and 80%.⁵⁻⁷ Even after a radical operation, there is local recurrence in about 5% to 10% of patients, although the impact of this on survival remains uncertain.^{8,9} Some previous reports^{5,10-13} indicate that this is a grave prognostic sign, but others disagree.¹⁴⁻¹⁹ Evans⁹ has recently suggested the importance of distinguishing two manifestations of locally recurrent disease stating that "Local recurrence following radical surgery is a grave sign, but local recurrence following limited surgery, which is labelled 'local persistence' is often an innocent event".

With this in mind we have analysed the impact on the prognosis of local recurrence using a prospectively compiled database of 173 consecutive patients with localised STS of the limbs or trunk. We classified local recurrences according to whether they were present before referral to us or after definitive surgery at our hospitals.

PATIENTS AND METHODS

Between 1976 and 1992, 214 patients were referred to the Departments of Orthopaedic Surgery in the Osaka University Medical School and the Osaka Medical Center for Cancer and Cardiovascular Diseases, with STS of the limbs or trunk. Of these, 41 were excluded from the study: 26 had distant metastasis when first seen, four had definitive surgery performed elsewhere, five had an extra-abdominal desmoid tumour, five an infantile fibrosarcoma and one was lost to follow-up. The remaining 173 patients were assessed and their clinicopathological characteristics are summarised in Table I.

There were 101 males and 72 females with a median age of 44 years (3 to 85). They were divided into three groups as follows: group A ($n = 78$), initially treated at our hospi-

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Table I. Details of 173 patients with soft-tissue sarcoma, by number and *percentage*

Characteristics		
Gender		
Male	101	58
Female	72	42
Median age in years (range)	44	(3 to 85)
Status at presentation		
Primary	78	45
Immediately after resection elsewhere	49	28
Locally recurrent	46	27
Primary site		
Upper limb	25	14
Lower limb	97	56
Trunk*	51	30
Tumour size (cm)		
≤5	64	37
>5	103	60
Unknown	6	3
Tumour depth		
Superficial	38	22
Deep	114	66
Unknown	21	12
Histological grade		
Low (G1)	48	28
Intermediate (G2)	49	28
High (G3)	76	44
Histological type		
Malignant fibrous histiocytoma	51	30
Liposarcoma	31	18
Synovial sarcoma	25	15
Malignant peripheral nerve-sheath tumour	15	9
Dermatofibrosarcoma protuberans	9	5
Leiomyosarcoma	6	3
Rhabdomyosarcoma	6	3
Fibrosarcoma	4	2
Others	26	15

* including limb girdles

tals; group B (n = 49), referred to our hospitals immediately after inadequate surgery elsewhere; and group C (n = 46), treated after local recurrence following previous surgery elsewhere. The lower limbs were the site of the primary tumour in 97 patients, the trunk including the limb girdles in 51, and the upper limbs in 25. The size of the tumour was defined as its maximum diameter. Its depth was estimated relative to the neighbouring fascia and defined as superficial or deep.

The histological diagnosis according to the criteria of Enzinger and Weiss,²⁰ was malignant fibrous histiocytoma (MFH) in 51 patients, liposarcoma in 31, synovial sarcoma in 25, malignant peripheral nerve-sheath tumour (MPNST) in 15, dermatofibrosarcoma protuberans in 9, leiomyosarcoma in 6, rhabdomyosarcoma in 6, fibrosarcoma in 4, and other types of sarcoma in 26. The distribution of the histological grading, based on our criteria previously described,^{6,21} was low grade (G1) in 48 tumours, intermediate grade (G2) in 49, and high grade (G3) in 76. The clinical stages were determined according to the American Joint Committee (AJC) staging system²² as stage Ia in 15 cases, Ib in 29, IIa in 20, IIb in 27, IIIa in 26, IIIb in 43, and IVa with regional lymph node metastasis in 7.

Table II. Types of treatment performed in 173 patients, by number and *percentage*

Treatment		
Surgical procedure		
Wide local excision	140	81
Marginal excision	15	9
Intralesional excision	4	2
Amputation/or disarticulation	14	8
Adjuvant radiotherapy		
Postoperatively (+)	30	17
Preoperatively (+)	7	4
Pre- and postoperatively (+)	2	1
None	134	78
Adjuvant chemotherapy		
Pre- and postoperatively (+)	89	51
Postoperatively (+)	31	18
Preoperatively (+)	20	12
None	33	19

Table II gives details of the surgical and adjuvant treatment performed. The definitive surgery at our hospitals was carried out with the intention of achieving a cure. It included wide local excision in 140 patients, marginal excision in 15, intralesional excision in 4, and wide amputation/or disarticulation in 14. Most patients (92%) had limb-sparing surgery. The surgical margin was evaluated in all except 13 patients by examination of the resected specimens and was defined as adequate for those with more than a wide margin in all planes (n = 126) and inadequate for those with a marginal or intralesional margin in at least one plane (n = 34). Thirty-nine patients received adjuvant radiotherapy. This was after operation in 30, before in seven, and both before and after in two patients for tumours which were unlikely to have local control by surgery alone. The total doses of radiotherapy used ranged from 28 to 70 Gy (mean 46.7). Adjuvant chemotherapy was used in 140 patients: both before and after operation in 89, before operation only in 20 and after only in 31. The chemotherapeutic regimens varied, but mostly included doxorubicin as well as ifosfamide, vincristine, and cisplatin.

Statistical analysis. The follow-up period for all patients was calculated from the date of the initial definitive operation and ranged from 5 to 216 months (median: 48 months for all patients, 59 months for survivors). Actuarial survival curves were constructed using the method of Kaplan-Meier,²³ and the log-rank test for survival analysis²⁴ was used to estimate the prognostic significance of the clinicopathological variables. The presence of local recurrence before referral or after definitive surgery at our hospitals was analysed separately.

We performed multivariate analysis using Cox's proportional hazards model²⁵ to identify the independent prognostic factors. For variables analysed by multivariate analysis, relative risks with 95% confidence intervals (CI) were calculated. These analyses were performed using JMP statistical computer software version 3.1 (SAS Institute, Cary, North Carolina).

Fig. 1

Actuarial overall survival curves for each group according to the status at initial presentation. Group A, those who were initially treated ($n = 78$); group B, those referred immediately after inadequate surgery elsewhere ($n = 49$); group C, those who were treated after local recurrence after previous surgery elsewhere ($n = 46$). The dots represent censored observations.

Fig. 2

Actuarial overall survival curves for patients with or without local recurrence after definitive surgery at our hospitals. The dots represent censored observations.

RESULTS

The actuarial overall five- and ten-year survival rates were 75.2% (95% CI 67.9% to 82.4%) and 68.0% (95% CI 58.6% to 77.4%), respectively. Local recurrence after definitive surgery occurred in 25 of the 173 patients (14.5%). The median time to development of local recurrence after definitive surgery was 20 months (3 to 97). Assessment of recurrence according to the groups previously defined showed the local rate in group C to be 28.3%, relatively higher than in group A (9.0%) and group B (10.2%). The

Table III. Univariate analysis for prognostic factors

Variables	Five-year survival rate (%)	p value
Gender		
Male	74.8	0.35
Female	76.2	
Age (yr)		
<45	76.8	0.33
≥45	73.3	
Primary site		
Upper limb	68.7	0.76
Lower limb	79.5	
Trunk*	69.3	
Tumour size (cm)		
≤5	90.3	0.002
>5	66.7	
Tumour depth		
Superficial	96.6	0.003
Deep	69.4	
Histological grade		
Low (G1)	95.5	0.0002
Intermediate (G2)	78.9	
High (G3)	60.1	
Histological type		
Malignant fibrous histiocytoma	78.9	0.33
Liposarcoma	86.7	
Synovial sarcoma	66.4	
Malignant peripheral nerve-sheath tumour	59.1	
Dermatofibrosarcoma protuberans	100.0	
Leiomyosarcoma	83.3	
Rhabdomyosarcoma	50.0	
Fibrosarcoma	75.0	
Others	67.3	
Surgical margin		
Adequate	81.7	0.0001
Inadequate	44.6	
Local recurrence at initial presentation		
Absent	74.1	0.84
Present	78.7	
After definitive surgery		
Absent	79.5	0.006
Present	54.1	

* including limb girdles

actuarial overall survival rate of group C, however, was not significantly worse than that of groups A and B (Fig. 1). To estimate the prognostic significance of local recurrence before referral to our hospitals, groups A and B were summed, and their overall survival rate compared with that of group C. Again there was no significant difference in survival between group A+B and group C.

Univariate analysis for prognostic factors. Table III gives the results of univariate survival analysis according to various clinicopathological factors. The histological grade (G1 v G2 v G3, $p = 0.0002$), the size of the tumour (≤ 5 cm v > 5 cm, $p = 0.002$), the depth of the lesion (superficial v deep, $p = 0.003$), and the surgical margin (adequate v inadequate, $p = 0.0001$) were the significant prognostic factors. Local recurrence after definitive surgery at our hospitals (absent v present, $p = 0.006$) was also significantly associated with patient survival (Fig. 2), whereas the presence

Table IV. Multivariate analysis for prognostic factors

Variables	Risk ratio	95% CI
Tumour size (cm)		
≤5		
>5	3.12	1.26 to 9.62
Tumour depth		
Superficial		
Deep	6.35	1.29 to 115
Histological grade		
Low (G1)		
Intermediate (G2)	8.72	1.56 to 163
High (G3)	2.47	1.17 to 5.69
Surgical margin		
Adequate		
Inadequate	3.62	1.49 to 8.50
Local recurrence		
At initial presentation		
Absent		
Present	1.09	0.45 to 2.44
After definitive surgery		
Absent		
Present	0.95	0.37 to 2.36

of local recurrence at the initial presentation did not affect survival.

Multivariate analysis for prognostic factors. Using the data for the 143 patients for whom we had full clinical information, the five significant prognostic factors selected in the univariate analysis together with local recurrence at initial presentation were subjected to multivariate analysis. The histological grade, the size of the tumour, its depth, and surgical margin proved to be the significant prognostic factors (Table IV), as has previously been shown in many other studies.^{5,6,11,19,26-31} Neither local recurrence at initial presentation nor after definitive surgery at our hospitals had prognostic significance in the multivariate analysis.

DISCUSSION

It is agreed that local control of primary STS is essential. Wide local excision with or without adjuvant radiotherapy is now standard for lesions in the limbs in order to avoid amputation. Inadequate surgery is still frequently performed, however, before proper consultation with specialist centres, resulting in a high incidence of local recurrence, which has long been considered to be an ominous prognostic sign.^{5,10-13} Several recent reports, however, have suggested that local recurrence does not adversely affect survival,¹⁴⁻¹⁹ but Pisters et al³⁰ have recently indicated that patients with locally recurrent disease when first seen are at increased risk of subsequent local recurrence and of death from the disease.

As Evans⁹ has pointed out, there are two patterns of local recurrence: first, that following a limited operation with an inadequate surgical margin, so-called 'local persistence', and secondly local recurrence after radical surgery with an adequate surgical margin. We have confirmed that the former type does not affect patient survival. Initial pre-

sentation to us with local recurrence after inadequate surgery elsewhere, however, was associated with a subsequent higher rate of local recurrence than patients presenting primarily to us (28.3% v 9.0%). Local recurrence after a definitive operation aimed at cure at our hospitals, however, was a significantly unfavourable prognostic factor in univariate analysis, but not in multivariate analysis. This is because other independent prognostic factors such as the histological grade, the size and depth of the tumour and the surgical margin influence the prognosis to a much greater degree. Gaynor et al²⁸ also suggested that local recurrence may be an unfavourable prognostic factor, but only in patients whose tumours had become more aggressive at the time of the local recurrence. Thus, local recurrence appears to be a marker for, rather than a cause of, the poor prognosis, and, indeed, a significant risk factor in the survival of patients with small and/or low-grade tumours.^{32,33}

We have previously reported that increases in cellularity and mitotic counts occurring during repeated recurrences of STS indicate an unfavourable prognosis.³⁴ Wide local excision with an adequate surgical margin is thus considered critical for patients with small and/or low-grade tumours in order to improve their prognosis. In patients with large and/or high-grade tumours which are both locally and distantly aggressive,^{16,17} however, local control by wide local excision with or without radiotherapy does not necessarily contribute to an improvement in survival when the patients already require maximum treatment combined with adjuvant chemotherapy to prevent distant metastases.

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